SUMMARY

This is a FY-16 High Priority "For Cause" assignment from the CDER, Division of Clinical Compliance Evaluation to conduct an inspection of Kang Zhang, M.D., Ph.D., Sponsor-Investigator per assignment that originated in a memorandum dated April 8, 2016, (FACTS Assignment # 11632348). The inspection focused on Sponsor-Investigator responsibilities regarding Protocol # (b) (4) , (b) (4) " under IND # (b) (4) . The inspection was performed in accordance with the Sponsor and Clinical Investigator Compliance Programs 7348.810 and 7348.811.

There are no previous inspectional history records for Kang Zhang, M.D., Ph.D. as a Sponsor-Investigator and a Clinical Investigator.

The current inspection covered a human clinical trial conducted at Shiley Eye Center-UCSD in La Jolla, CA, (b) (4) The current inspection revealed Sponsor and Clinical Investigator objectionable conditions. At the close of the inspection, an FDA483 was issued to Dr. Zhang for the following: 1) Failure to monitor all investigational sites; 2) Failure to submit to FDA an annual report in 2012, 2014, 2015, and 2016; 3) Failure to suspend enrollment during an IRB suspension period; 4) Failure to follow the investigational plan such as including subjects that did not meet inclusion criteria, conduct/collect protocol required ophthalmologic examinations, and failure to conduct early termination visits; 5) All versions of the Informed Consent form does not contain the required www.ClinicalTrials.gov statement; 6) Failure to retain all required records during the retention period; & 7) Investigational drug disposition records are not adequate.

There were several delays in providing the requested records for review; records were repeatedly requested to several responsible individuals in the firm and not provided for lengthy periods of time.

There were no refusals and no samples collected.

ADMINISTRATIVE DATA

Inspected firm:	Kang Zhang, M.D., Ph.D.
Location:	9415 Campus Point Dr., Room E214 La Jolla, CA 92093-0946
Phone:	858-246-0814
FAX:	858-246-0873
Mailing address:	9415 Campus Point Dr., Room E214 La Jolla, CA 92093-0946
Dates of inspection:	7/14/2016-7/15/2016 , 7/18/2016-7/22/2016 , 7/25/2016, 7/28/2016, 8/1/2016
Days in the facility:	10
Participants:	**Natalie J Ayoub, Investigator - Dedicated Food Cadre**

On 07/11/16, I pre-announced the inspection of Kang Zhang, M.D., Ph.D. to his Research Coordinator Cindy Wen. She informed me that he will not be available until 07/28/16. I told her that I cannot delay the inspection for 2 ½ weeks. Ms. Wen was unaware of the requirements for an FDA inspection, so I explained to her the records needed and the inspection process. I scheduled the inspection to begin on 07/14/16. She then informed me that Dr. Zhang would be available to meet with me on 07/18/16.

On 07/14/16, I arrived at UCSD - Shiley Eye Center located at 9415 Campus Point Dr., Room E214, La Jolla, CA 92093. I presented my credentials and issued an FDA 482, Notice of Inspection, to Cindy H. Wen, Research Coordinator.

Dr. Zhang was available for approximately an hour to speak to me only on 07/19/16, 07/25/16 and the close-out on 08/01/16.

Any correspondence should be addressed to:

Dr. Kang (NMI) Zhang, M.D., Ph.D.

Shiley Eye Center – UCSD

9415 Campus Point Dr., Room E214
La Jolla, CA 92093

SPONSOR

ORGANIZATION AND PERSONNEL

A Research Payment and Supply Agreement was signed by a (b) (4) representative, UCSD representative, and the Sponsor-Investigator Dr. Kang Zhang on 07/29/11 as seen in Exhibit 1. The Agreement documents that (b) (4) . is the study drug provider and is responsible for providing funding to conduct the clinical study. Also, the Agreement documents that Dr. Zhang is responsible for regulatory obligations as the Sponsor and is the Sponsor-Investigator of the (b) (4) clinical trial. (b) (4) approval of the (b) (4) protocol Version 1 (02/24/11) can be seen in Exhibit 17 pg. 56-57.

Dr. Kang Zhang submitted an FDA 1571 Form, Investigational New Drug Application (IND), dated 02/24/11, which documented himself as the Sponsor-Investigator and Monitor of IND (b) (4) (Exhibit 2). Protocol # (b) (4) , (b) (4) was added to IND (b) (4) . The IND was initially submitted to FDA on 07/16/08 for a clinical trial under Protocol "(b) (4) ". A letter regarding the (b) (4) submission can be seen in Exhibit 3. The (b) (4) study was added to IND (b) (4) as seen in a letter dated 04/22/11 addressed to FDA (Exhibit 4). Dr. Zhang's FDA correspondence binder section contained an FDA response letter regarding the IND submission for the (b) (4) protocol with comments regarding the protocol (Exhibit 5). Dr. Zhang did not respond to FDA regarding the comments and did not address or change the protocol per the recommendations. The FDA correspondence binder section also included an Overdue Annual Report letter dated 08/19/13 as seen in Exhibit 6. Dr. Zhang turned in Annual Report for IND (b) (4) , dated 12/17/13, as seen in Exhibit 7. Refer to **Observation 2** for issues regarding failing to submit an annual report in 2012, 2014, 2015, and 2016.

The (b) (4) clinical trial was conducted at (b) (4) study sites, with Dr. Zhang's study site acting as the main site. The study sites and associated Principal Investigator can be seen below:

1) MAIN SITE/SPONSOR SITE:
   Shiley Eye Center – UCSD
   9415 Campus Point Dr., San Diego, CA 92093
   Principal Investigator: Kang Zhang, M.D., Ph.D

(b) (4)

(b) (4)

When reviewing records, I observed several records to list (b) (4) as Sub-Investigators and other records stating they are Principal Investigators. For example, Dr. Zhang's FDA 1572 form lists (b) (4) as Sub-Investigators (Exhibit 8). However, (b) (4) has (b) (4) own FDA 1572 form documenting that he is the Principal Investigator at the (b) (4) (Exhibit 9). Also, (b) (4) filled out one FDA 1572 Form documenting that they are (b) (4) the Principal Investigator at the (b) (4) (Exhibit 10). An IRB study approval letter for the (b) (4) states that the IRB "(b) (4) " (Exhibit 11 pg. 14). Additionally, a Clinical Research Collaboration Agreement between UCSD and (b) (4) identified as (b) (4) documents (b) (4) as the Subrecipient PI and lists (b) (4) responsibilities (Exhibit 12). A similar agreement was not observed for the (b) (4). On 08/01/16, I asked Dr. Zhang for clarification regarding who the Principal Investigators are for each site. He told me (b) (4) is the Principal Investigator at the (b) (4) . He continued to tell me that (b) (4) is the Principal Investigator and (b) (4) is the Co-Investigator at the (b) (4). The information was documented in an Affidavit; however, Dr. Zhang could not sign the Affidavit without UCSD regulatory review per UCSD policy.

REGISTRATION OF STUDIES ON CLINICALTRIALS.GOV

The firm does not have procedures for registering clinical trials. The (b) (4) Study began in 2011. Ms. Wen supplied me with documentation showing the (b) (4) Study was registered at www.clinicaltrials.gov (Exhibit 13).

The IRB informed consent forms did not include the required statement regarding clinicaltrials.gov (Refer to **Observation 5**).

SELECTION AND MONITORING OF CLINICAL INVESTIGATORS

There were (b) (4) sub-sites conducting the clinical trial located at the following locations:

(b) (4)

(b) (4)

Dr. (b) (4), M.D. was the Principal Investigator at the (b) (4). Dr. (b) (4) was the Principal Investigator at the (b) (4). Dr. (b) (4) is the Co-Investigator at the (b) (4).

I asked Dr. Zhang how he selected clinical investigators for the study and how he determined their qualifications. He told me that he met the (b) (4) clinical investigators through two large (b) (4) studies that they all participated in. He stated they were all in the (b) (4) and (b) (4) study as a Principal Investigator. Dr. Zhang got to know the clinical investigators through the (b) (4) investigator meetings they attended together. Dr. Zhang added that the clinical investigators all had conducted studies involving (b) (4). On 07/19/16, I asked Dr. Zhang how the clinical investigators were trained on the protocol. He told me that they were all self-trained. He stated that since the investigational drug is an approved drug, the clinical investigators at the sub-site are already familiar with the use and practiced standard practice of care when using the drug. Documentation that their training was self-taught can be seen in the Training Log in Exhibit 27.

On 07/19/16, I asked Dr. Zhang how information, protocol versions, and investigator brochures were provided to the Clinical Investigators at the sub-sites. He told me that he would provide information via conference calls and e-mails. He added that progress updates were conducted (b) (4) with the sub-sites. I asked him if he has any documentation regarding the communication. I also requested the sub-sites Principal Investigator's FDA 1572 forms and financial disclosure forms. He told me that he should have documentation but would have to look for it since the study closed approximately 2 years ago. I requested the records during all following days that I visited the study site. Ms. Wen continued to tell me they are still obtaining the records.

I met with Dr. Zhang again on 07/25/16 and asked for the records. He stated that Principal Investigator and Research Coordinator from one of the sub-sites were out of town on vacation. He continued to tell me that it is the summer time, which makes it difficult to obtain the records I requested. He added that it was a bad time to conduct the inspection since it is the summer and this inspection is interfering with his vacation plans to China. I told him that the records I requested were to be maintained at the sponsor site for the required period of time documented in the regulations. I added that the FDA 1572s forms and financial disclosure forms were to be obtained, reviewed, and verified to be adequate prior to starting the study; therefore, those records should be in his possession. Additionally, all e-mails and meeting minutes should have been maintained with the sponsor records. I continued to tell him that I pre-announced the inspection 3 days prior to arriving and have been conducting the inspection for a week and a half, which should have been adequate time to obtain the records. Dr. Zhang stated that he will have the records available to me by the end of the week. I told him that I will come back and review any remaining records on 07/28/16 and missing records can be sent to the FDA reviewer within 15 business days of the close-out.

Dr. Zhang did not obtain the Clinical Investigator's FDA 1572 Forms prior to initiating the study. During the inspection, the Research Coordinators got in contact with the sub-sites and requested the FDA 1572. On 07/28/16, Ms. Wen told me the FDA 1572s and Correspondence with the sub-sites had been collected and organized in a binder for my review. A review of the binder was conducted revealing the following:

- **FDA 1572 forms**: The FDA 1572 for Dr. (b) (4) can be seen in Exhibit 9. The FDA 1572 for Dr. (b) (4) and Dr. (b) (4) can be seen in Exhibit 10. During the close-out meeting, a discussion regarding conflicting information and Principal Investigator responsibility was addressed (Refer to **General Discussion with Management** section).
- **Financial Disclosure**: An e-mail correspondence dated 07/19/16 associated with the (b) (4) sub-sites documents that no financial disclosure forms were collected because the investigators Dr. (b) (4) and Dr. (b) (4) did not have anything to disclose (Exhibit 14).Dr. Zhang did not have any documentation of financial disclosure or rational for a lack of financial disclosure from Dr. (b) (4) . Refer to **General Discussion with Management** section regarding lack of financial disclosure forms from the Clinical Investigators from each sub-site.
- **FDA 1571**: The Sponsor binder had documentation of an FDA 1571 form filled out by Dr. (b) (4) (Exhibit 15). The form documents Dr. Zhang as being responsible for monitoring. During the close-out meeting, a discussion regarding conflicting information regarding roles and Sponsor responsibility was addressed (Refer to **General Discussion with Management**).
- **Correspondence**:
  - Correspondence obtained by Ms. Wen during the study from the sub-sites was e-mail correspondence between Dr. Zhang's site and the sub-site and IRB correspondence. The correspondence supplied to me includes mainly IRB approval letters obtained from the sub-sites and an enrollment update e-mail.

    All supplied e-mail correspondence and IRB correspondence records with Dr. (b) (4) at (b) (4) can be seen in Exhibit 16.

    All supplied e-mail correspondence and IRB correspondence records with Dr. (b) (4) and Dr. (b) (4) at (b) (4) can be seen in Exhibit 11.

  - (b) (4) sub-sites used the same IRB board, (b) (4) . The IRB study approval letters for (b) (4) sub-sites document that Protocol (b) (4)) Version 1 is approved and used in the study (Exhibits 11 pg.14 & 16 pg. 73). The Version 1 Protocol used at Dr. Zhang's site is dated 02/24/11 as seen in Exhibit 43. A different version of the protocol was used at the main site than the sub-sites. Based on the e-mail correspondence, it appears that the sub-sites used a different version of the Protocol than the main site until Amendment 2 was forwarded to them. I observed an IRB approval letter, dated 02/04/13, for Revised Protocol (b) (4) Incorporating Amendment 1 for the (b) (4) site as seen in Exhibit 16 pg. 17. I did not see any IRB approval letters for a protocol amendment in the (b) (4) correspondence records supplied to me (Exhibit 11). The main sites Protocol

Amendment 2 is dated 04-05-12 as seen in Exhibit 44. This discrepancy is documented in Sponsor correspondence e-mails with the sub-sites seen under the bullet point below:

- E-mail correspondence, dated 09/17/12, between Dr. Zhang's study coordinator Anya Morgan and the study coordinators at the sub-sites (b) (4) and (b) (4) can be seen in Exhibit 17 pg.12-13. The correspondence shows that Ms. (b) (4) updated the sub-sites with the Protocol Version 2 amendment changes implemented at the main site.

- E-mail correspondence, dated 01/28/13-01/30/13, between Ms. Wen, the sub-sites IRB board member from (b) (4), and a (b) (4) representative (b) (4) can be seen in Exhibit 17 pg. 4-11. The e-mail describes the discrepancy issue as, "(b) (4)".

- Ms. Wen also put together some e-mail correspondence between the sub-sites and (b) (4). All Sponsor correspondence records were collected and can be seen in Exhibit 17. The Sponsor correspondence documents protocol amendment distribution and issues regarding it. The correspondence records documents that amendments made on the sub-site version of the protocol were not the same as the protocol used at the main site as seen in Exhibit 17 pg. 4 & Exhibit 38 pg. 9. The amendments from the sub-site's protocol and main site's protocol were combined to create Version 3.5 of the protocol. It is unclear if Version 2 and Version 1 from the mainsite is the same as the one used at the sub-sites.

- The correspondence does not document distribution of the 4 versions of Investigator Brochures observed at the main site. I asked Dr. Zhang stated that (b) (4) supplied him with the Investigator Brochures and he was responsible for supplying it to them. He stated he thinks he supplied the Investigator Brochures to the sub-sites; however, there was no documentation of the distribution in the Sponsor correspondence section (Refer to **General Discussion with Management** section).Documentation that Dr. Zhang received the Investigator Brochure Version 9,10,11, and 12 from the study drug supplier (b) (4) can be seen in Exhibit 18. Investigator Brochure Version 9, 10, and 11 can be seen in Exhibit 19-21. Dr. Zhang received Investigator Brochure Version 12 per Exhibit 18 pg. 1-2; however, he did not have a copy of it on hand. An electronic version of the IB was supplied to me by

Ms. Wen, but it was only the signed receipt record.

The Sponsor Dr. Kang Zhang is documented to be the monitor on the FDA 1571 form as seen in Exhibit 2. Additionally, correspondence with (b) (4) dated 07/08/11 documents a (b) (4) representative informing the Research Coordinator that the (b) (4) research coordinators at Dr. Zhang's site are responsible for monitoring as seen in Exhibit 17 pg. 41-42. On 07/19/16, I asked Dr. Zhang if his site and the sub-sites were monitored. He told me that oversight was assumed to be self-monitored at all study sites. He told me he assumed that all sub-sites would follow procedures because they are large research facilities. Refer to **Observation 1**. He stated that the sub-sites did not report to him any serious adverse events. Due to the lack of monitoring, the sponsor did not verify the clinical investigators complied with the investigational plan and FDA regulations. No clinical investigators from the sub-sites were identified as non-complaint. The sponsor did not have any documentation from the sub-sites of addressing and handling serious deviations from the approved investigational plan. The sponsor had incomplete records from the sub-sites; therefore, I was unable to determine if serious deviations from the investigational plan occurred at the sub-sites.

SELECTION OF MONITORS

There is no Monitoring Plan. There are no monitoring procedures. There are no monitors selected to monitor the Study. (Refer to **Observation 1**).

MONITORING PROCEDURES AND ACTIVITIES

There are no formal procedures for monitoring. There is no documentation of what data monitoring (Refer to **Observation 1**).

QUALITY ASSURANCE

There is no Quality Assurance Unit.

SAFETY AND ADVERSE EVENT REPORTING

The main study site had two Serious Adverse Events and one MedWatch report occurred during the study. According to Dr. Zhang, the sub-sites did not have any Serious Adverse Events occur. The protocol documents the timeframe requirements for the sub-sites to notify Dr. Zhang as the sponsor for any serious adverse event reports. The protocol also documents timeframes to notify the study drug supplier (b) (4) regarding any Unanticipated Adverse Events. Dr. Zhang told me that none of the Serious Adverse Events that occurred at his site met the criteria of an IND Safety Report to be submitted to FDA. Dr. Zhang did not maintain any documentation from the sub-sites, such as adverse event logs and regulatory records, to verify if any serious adverse events occurred there (Refer to **Data Collection and Handling** section).

Documentation for the two Serious Adverse Events and one MedWatch report can be seen in the following Exhibits:

- Subject (b) (6) : The subject underwent corrective surgery involving cataract extraction and intraocular lens implantation due to a rent in the posterior capsule of the lens in the left eye from the Day 0 injection. The Day 0 injection was administered by Dr. Zhang. The subject sent a complaint to the UCSD IRB who had oversight of Dr. Zhang's study site. Documentation of the complaint and Serious Adverse Event can be seen in Exhibit 22. Subject (b) (6) did not meet inclusion criteria (Refer to **Observation 4 section A(a)**). Also, the EDTRS BCVA, SD-OCT, and FA protocol required procedures were not conducted on Day 0 (Refer to **Observation 4 section C**).
- Subject (b) (6) : The subject suffered from a myocardial infarction prior to the Month 2 visit. An Adverse Event report was submitted to the study drug supplier (b) (4) as seen in Exhibit 23. Dr. Zhang determined the serious adverse event was not associated with the study drug. The subject continued the study until the Month 5 visit due to pre-mature closure of the study.
- Subject (b) (6) : The subject withdrew consent on 05/04/12 because the subject entered hospice care for uncontrolled diabetes. The research coordinator filled out a MedWatch report as seen in Exhibit 24.

DATA COLLECTION AND HANDLING

There are no subject data tabulations to review against the sponsor's data. Ms. Wen and Dr. Zhang informed me that the study was pre-maturely stopped due to not meeting enrollment timeframes. Dr. Zhang told me that he plans on withdrawing the IND. There are no Case Report Forms (CRFs) developed to transcribe or collect data.

Source documents were created by the Sponsor and supplied to the sub-sites. Source documents are hand written by the sub-site and were scanned to Dr. Zhang upon completion of the study. Source documents for Dr. Zhang's site were maintained in individual subject binders. (b) (4) enrolled (b) (4) subjects. (b) (4) enrolled (b) (4) subjects, but source documents for (b) (4) out of (b) (4) of the subjects were observed to be maintained. The only records obtained from the sub-site were study visit source documents. Dr. Zhang did not collect from the sub-sites baseline exam records, ophthalmologic evaluations, SD-OCT results, FA results, Adverse Event listings, Concomitant medication lists, enrollment logs, drug accountability records, and informs consent forms documenting version used and date it was signed. Therefore, data tabulations could not and was not performed for each subject.

On 07/19/16, I asked Dr. Zhang if he had Standard Operating Procedures (SOPs) regarding his Sponsor responsibilities. He told me he would look into it. He did not supply me with Sponsor SOPs. I asked Ms. Wen if Dr. Zhang has Sponsor SOPs. She told me the records provided to me were all they had. Sponsor SOPs were not in the binders reviewed; therefore, it appears that Dr. Zhang did not have any written procedures regarding his sponsor responsibilities.

Dr. Zhang did not properly close out the study with the IRB at the main site and sub-sites. A close out letter was not sent to the UCSD IRB board for his own study site; therefore, the study was withdrawn (Exhibit 41-42). Dr. Zhang did not submit protocol progress reports or a study closure report to the sub-sites IRB; therefore, the IRB suspended the study (Exhibit 11 pg.1-3 & 16 pg. 1-6). An e-mail correspondence, dated 03/14/13, between Ms. Wen, (b) (4) , and (b) (4) regarding study closure can be seen in Exhibit 25. The e-mail correspondence between Ms. Wen and a representative from (b) (4) documents that the representative informed Ms. Wen the IND FDA 1571 for (b) (4) belongs to (b) (4) , so he does not believe Dr. Zhang needs to close it out with the FDA. "(b) (4) " (Exhibit 25 pg. 2). The attachment for how (b) (4) needs to get closed out was not attached, but based on this correspondence it appears that Dr. Zhang was obligated to close out the (b) (4) IND portion with the FDA. Ms. Wen interpreted it that (b) (4) said the IND does not need to be closed out with the FDA as seen in Exhibit 25 pg. 1. This is the rationale Ms. Wen supplied to me to show why the IND was not closed with the FDA. At the time of the inspection, a study-close out or final report was created and conducted.

RECORD RETENSION

The study site did not collect and maintain all required Sponsor records prior to the inspection. Records such as FDA 1572 Forms, financial disclosure records, and sponsor correspondence records documenting providing Clinical Investigators with the protocol were requested during the inspection by the Sponsor to the sub-sites. According to Ms. Wen, the Sponsor regulatory binder is stored onsite at Shiley Eye Center.

FINANCIAL DISCLOSURE

Financial Disclosures were not obtained by Dr. Zhang for all clinical investigators participating. Refer to **General Discussion with Management** section.

ELECTRONIC RECORDS

All source data was documented on paper forms and was present in the clinic charts.

TEST ARTICLE

Test articles were supplied by (b) (4) , the manufacturer of (b) (4) . Documentation of storage temperature and acceptable excursions time-temperature frames were sent to the Sponsor in a Memo from the study drug supplier (b) (4) as seen in Exhibit 17 pg. 43. Any storage temperature excursions exceeding the timeframes were to be reported to (b) (4) per the Memo. Documentation of distribution of the Memo to the sub-sites was not documented. Additionally, this requirement was not included in all versions of the Protocol.

Investigational drug distribution and accountability to each sub-site is documented to be the responsibility of the drug manufacturer (b) (4) per a signed contract with them as seen in Exhibit 1 pg. 5.

CLINICAL INVESTIGATOR

AUTHORITY AND ADMINISTRATION

A copy of Dr. Zhang's FDA 1572 – Statement of Investigator Form can be seen in Exhibit 8. A list of Clinical Research and Clinical Trials Dr. Kang Zhang has conducted can be seen in his Curriculum Vitae in Exhibit 26.

All study visits were conducted at Shiley Eye Center – UCSD located at 9415 Campus Point Dr., La Jolla, CA 92093. Refer to Selection and Monitoring of Clinical Investigators section for how information was provided. Training for all employees on the study was self-taught. Training log documenting that training on the protocol was self-taught can be seen in Exhibit 27.

Delegation Log can be seen in Exhibit 27.
Enrollment Log can be seen in Exhibit 28.

The majority of the subjects were recruited from a different study called "(b) (4) ". Other subjects were recruited from the clinic at the UCSD hospital. Old and new patients from the UCSD hospital clinic were recruited.

A laboratory was used for genetic research conducted by Dr. Zhang. The on-site laboratory used was:
(b) (4)

The dates for IRB approval, IRB enrollment suspension, and IRB approval letters can be seen in the table below:

Document	IRB Approval Date	Exhibit #
(b) (4) project approval Informed Consent Form – Version 2	04/21/11	Exhibit 29
(b) (4) study pending approval letter	04/22/11	Exhibit 30
(b) (4) project approval Protocol Version 1 (02/24/11)	05/13/11	Exhibit 31
Conflict of Interest Clarification	09/09/11	Exhibit 32
Subject Complaint/SAE Clarification	01/10/12	Exhibit 33
Acknowledgement of Protocol	02/23/12	Exhibit 34

Deviations		
Continuing Review of Study Approval	04/05/12	Exhibit 35
Amended Protocol Version 2 (04/05/12) Informed Consent Form – Version 3	08/03/12	Exhibit 36
Study Enrollment Suspension Letter	12/13/12	Exhibit 37
Amended Protocol Version 3.5 Informed Consent Form – Version 4	03/21/13	Exhibit 38
Enrollment Hold lift Release of Informed Consent Form Version 4 for use	08/26/13	Exhibit 39
Continuing Review of Study Approval	03/20/14	Exhibit 40
Lack of Renewal of Approval notification or study close out	03/23/15	Exhibit 41
Study Withdrawn by IRB due to lack of communication	04/23/15	Exhibit 42

Note: The exhibits in the table below include correspondence between Dr. Zhang and the IRB.

The IRB initially approved the project on 04/21/11 pending submission of additional records from Dr. Zhang (Exhibit 29 & 30). The IRB sent another letter on 05/13/11 stating initial approval of the project can be granted; however, approval cannot be released until a contract between the sponsor and UCSD is in place (Exhibit 31). The IRB did not send an approval letter acknowledging the contract between the sponsor and UCSD which would release approval.

SUBJECTS	
First subject was screened:	08/15/11
First subject signed the informed consent:	08/15/11
First administration of the test article:	08/15/11
Last subject follow-up	01/27/14

PROTOCOL

During the study, three versions of the protocol were used. The two sub-sites used a different version of the protocol than Dr. Zhang's site until Version 3.5 was approved by the IRB. Refer to **Selection and Monitoring of Clinical Investigators** section. The three versions of the protocol used at Dr. Zhang's site are as follows:

- Protocol # (b) (4), (b) (4) Version 1(February 24, 2011) – Exhibit 43

- Protocol # (b) (4), (b) (4) Version 2/Amendment 1(April 5, 2012) – Exhibit 44
- Protocol # (b) (4), (b) (4) Version 3.5(June 22, 2011) – Exhibit 45

I asked Ms. Wen if there was a Version 3 that was approved. She told me that she is not sure why the protocol went from Version 2 to 3.5, but there was no version 3 that was implemented.

(b) (4) out of (b) (4) subjects did not meet the Inclusion Criteria listed. For (b) (4) out of (b) (4) subjects, Baseline or Day 0 protocol required examinations were not conducted. Also, early termination visit assessments were not conducted for four (4) subjects. Refer to **Observation 4** for protocol deviations that occurred during the study. During the record review, I observed multiple note to files regarding missed administration of the study drug despite meeting study drug administration criteria and lack of Intraocular Pressure (IOP) examinations after the study drug was administered. Refer to **General Discussion with Management** section.

The total number of subjects: screened - 12, enrolled - 12, and completed the study – 6.

INSTITUTIONAL REVIEW BOARD (IRB)

The IRB providing oversight for the (b) (4) Study is:
University of California, San Diego Institutional Review Board (UCSD IRB)
9500 Gilman Dr., La Jolla, CA 92093

The chairperson during the study was (b) (6), Ph.D. Director. The UCSD IRB does not disclose their IRB Roster. A Letter of Assurance regarding following IRB regulations can be seen in Exhibit 46.

IRB approval dates of the study, protocol amendments, and informed consent forms can be seen in the table under the **Authority and Administration** section. Personnel amendment requests and approved are not included in the table. All personnel amendment requests and approvals can be seen in Exhibit 47.A list of dates and documents regarding IRB submissions and responses can be seen in Exhibit 48.

UCSD Research Compliance Program conducted a review of the study twice and submitted a letter with findings on 03/09/12 and 11/13/14 as seen in Exhibit 49. On 07/20/15, the Research Compliance Program sent Dr. Zhang stating that he did not notify the IRB regarding several issues within 30 days of receipt of the 11/13/14 letter. On 07/30/15, Dr. Zhang submitted the requested records to the IRB. The IRB responded on 09/01/15 with an additional request. Dr. Zhang did not respond to the IRB until 07/13/16. The above correspondence can be seen in Exhibit 50.

The IRB suspended Dr. Zhang from new enrollment for all of the PI's active research trials at UCSD. The IRB also held amended Informed Consent Form Version 4 from use until the enrollment

was lifted. During the enrollment suspension period from 12/07/12 to 08/26/13, Dr. Zhang enrolled 3 subjects into the study. 2 out of 3 of the subjects used ICF Version 4. Refer to **Observation 3**.

HUMAN SUBJECTS' RECORDS

Informed Consent

During the study, there were 3 IRB approved Informed Consent Forms that were used:

- Informed Consent Form Version 2 – Exhibit 51
- Informed Consent Form Version 3 – Exhibit 52
- Informed Consent Form Version 4 – Exhibit 53

A 100% review was conducted of all subject Informed Consent Forms (ICFs). It appears that all subjects signed and dated their own consent forms. The ICFs were observed to be administered by the Research Coordinator (b) (6), (b) (6), Anya Morgan, (b) (6), or Cindy Wen.

Subject (b) (6) 's ICF form was not in the subject's binder and was not found prior to the close-out of the inspection (Refer to **Observation 6**). Also, ICF Version 4 was used to consent Subject (b) (6) and (b) (6) during the enrollment suspension period and prior to IRB authorized release (Refer to **Observation 3**).

All 3 IRB approved Informed Consent Forms used during the study did not contain the required www.ClinicalTrials.gov statement. Refer to **Observation 5**.

Source Documents

The investigator's source data records were organized in each subjects' own binder. The patient's medical folders were pulled so which were to contain Baseline required procedures. Source documentation observed for each subject generally contained original Informed Consent Forms, Adverse Event Log, Concomitant Medication Log, Study Visit records, Evaluation of Visual Acuity Assessment- Best Corrected Visual Acuity (ETDRS BCVA) examinations for both eyes, Spectral Domain Optical Coherence Tomography (SD-OCT), and Fluorescein Angiography (FA).

During the record review, I observed adverse events in the subject's visit assessment record, but it was not inputted in the adverse event log. Refer to **General Discussion with Management** regarding documentation of adverse events to verify proper monitoring and clinical investigator oversight occurred.

FINANCIAL DISCLOSURE

I observed that the Principal Investigator Dr. Khang had signed documents disclosing information about their financial interests to the IRB prior to the start of the study at the site. The IRB notified Dr. Zhang of a conflict of interest listed on the financial disclosure. The conflicting interest was

associated with Dr. Zhang receiving compensation for traveling to a speaking engagement on behalf of (b) (4). A letter to the IRB dated 08/19/11 stated Dr. Zhang will no longer receive reimbursement or conduct any speaking engagements. On 09/09/11, the IRB acknowledged his response. The IRB correspondence records can be seen in Exhibit 54.

ELECTRONIC RECORDS AND ELECTRONIC SIGNATURES

All source data was documented on paper forms and was present in the clinic charts. Electronic records and signatures were not captured for data collection.

TEST ARTICLE ACCOUNTABILITY

Per the protocol, the study drug is required to be (b) (4)

Based on (b) (4) Study Drug handling requirements, (b) (4) must be (b) (4) (Exhibit 17 pg. 43). Temperature excursions were observed to occur; however, none of them met the (b) (4) time frame. (b) (4) was notified for (b) (4) out of (b) (4) of the temperature excursion incidents. The (b) (4) notifications involved (b) (4) temperature excursion that occurred for less than (b) (4) hours on 05/28/12 and temperature excursion of (b) (4) over the weekend of 09/29/12-09/30/12 (Exhibit 55). A (b) (4) temperature excursion occurred over the weekend of 11/04/11-11/07/11 as seen in Exhibit 56. A (b) temperature excursion occurred on 09/08/11-09/09/11 as seen in Exhibit 57. The first drug shipment was received on 08/12/16 as seen in Exhibit 59 & 60.During the close-out, I discussed with Dr. Zhang the importance of storing the study drug at the appropriate temperature and notifying the drug supplier per their requirements. He stated he understood.

Temperature monitoring records were not retained after 07/19/13 (Exhibit 58) (Refer to **Observation 6**); therefore, I was unable to determine if additional temperature excursions occurred.

Study drug receipt was adequately documented in Receipt Letters and a Test Drug Accountability Log as seen in Exhibit 59. The study site did not adequately document the disposition of unused/expired study drugs from 4 separate lots (Refer to **Observation 7**).

(b) (4) lot that was unaccounted for was found by Ms. Wen and shown to me on 08/01/16. (b) (4) units of Lot (b) (4) are documented to not be used in the Test Drug Accountability Log as seen in Exhibit 60 pg. 7. She showed me the box and I counted (b) (4) units in box holding (b) (4) vial of the study drug. In a plastic bag contained (b) (4) syringes with the lot tag attached to it.

RECORDS CUSTODY AND RETENTION
Source documents and patient medical charts are stored onsite in a locked closet at Shiley Eye Center. Some of the older patient medical charts were stored at the record storage site (b) (4) .

Several source documents, Subject (b) (6) s Informed Consent Form, and Refrigerated Study Drug Temperature Log records were missing; therefore, they were not retained for the required retention period. Refer to **Observation 6.**

REPORTS TO SPONSOR
Dr. Zhang is the Sponsor-Investigator. He is responsible for all Sponsor requirements; however, not all requirements were met. Refer to **Observations 1-2** and **Data Collection and Handling** section.

MONITORING
As previously mentioned under the SPONSOR section of this report, there was no monitoring. Refer to **Observation 1**.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE
The FDA 483 was issued to Kang (NMI) Zhang, M.D. Ph.D., Sponsor-Investigator, who is the most responsible person. Cindy H. Wen, Clinical Research Coordinator was present during the closing meeting. I read the introductory paragraph on the FDA-483 form. I explained these were my observations and that upon further review they could be found to be violations to FDA regulations. I also explained regulatory sanctions available to the agency should the firm fail to correct violations to FDA regulations. The firm intends to send a written response within 15 business days.

Observations listed on form FDA 483
In relation to a clinical trial conducted under a protocol titled, Protocol #(b) (4) , "(b) (4)

Protocol Version 1, dated 02/24/11
Protocol Version 2, dated 04/05/12
Protocol Version 3.5, dated 01/28/13

SPONSOR

OBSERVATION 1
Failure to monitor the progress of an investigation conducted under your IND.

Specifically, there was no Monitoring Procedures/Plan or any documentation, such as monitoring reports or logs to show that the investigational sites were monitored. There was no documentation to verify that the investigational sites have conducted the clinical trials according to the protocol requirements.

Reference: 21 CFR 312.56(a)

Supporting Evidence and Relevance:
On 07/19/16, I asked Dr. Zhang if any monitoring was conducted at the main site and sub-sites. He told me that the Principal Investigators at each site were responsible for self-monitoring. He said that he assumed each sub-site would follow the procedures and protocol because they are large research facilities that have conducted many studies. I asked if he ever visited the sub-sites and monitored the sites. He said no. I asked if he hired a CRO. He said no. He told me that since the drug is an approved drug, the doctors at each site were expected to follow standard practice of care. He said monitoring was not required because the drug is approved and they are all experienced doctors following the standard protocol for the approved drug. I told him that an IND was submitted and a protocol for conducting the clinical trial was created. I told him since an IND and protocol procedures were in place, the clinical trial is to be conducted under the protocol and the federal regulations still apply to him monitoring the study. Dr. Zhang and Ms. Wen both addressed that they did not believe this study should have been under an IND. Dr. Zhang told me that (b) (4) would not allow him to conduct the drug study unless he became the Sponsor and filed an IND. He continued to tell me that he has done other studies regarding earlier use of (b) (4) . In those studies, Dr. Zhang said he did not have to file an IND or become the sponsor. Since no monitoring was conducted, the firm did not create and have any monitoring records.

A Research Payment and Supply Agreement with the investigational drug supplier (b) (4) signed on 07/29/11, defines, "The purpose of this Agreement is for (b) (4) to provide Study Drug and/or funding to Study Center to enable Kang Zhang, M.D., Ph.D, to conduct a clinical study and to provide (b) (4) with access to the study data and the final study report generated through the study." (Exhibit 1 pg. 2). The Sponsor-Investigator is defined to Kang Zhang M.D., Ph.D and employee of the Study Center University of California, San Diego. The Agreement continues to state under Section 2.5, "Study Center is responsible for all regulatory obligations imposed on the Sponsor. No such obligations are transferred to (b) (4) under this Agreement." (Exhibit 1 pg. 3). It continues to state under Section 2.7, "Sponsor-Investigator may involve Participating Sites to conduct the Study with the written approval of (b) (4) . […] In no event will any agreement with a Participating Site represent that either (b) (4) or any member of the (b) (4) is the Sponsor. Study Center and Sponsor-Investigator are solely responsible for overseeing the conduct of the Study at the Participating Sites." (Exhibit 1 pg. 3-4). The Agreement documents in several

locations that Dr. Kang Zhang is the Sponsor-Investigator and is responsible for Sponsor regulatory obligations including oversight or monitoring of the Participating Sites/Sub-sites. On 08/01/16, I asked Dr. Zang who the Principal Investigator is for the two sub-sites. He informed me that Dr. (b) (4) is the Principal Investigator for the (b) (4) study site. He stated that Dr. (b) (4) is the Principal Investigator for the (b) (4) study site, and Dr. (b) (4) is the Co-Investigator. (Refer to **Organization and Personnel** section under *SPONSOR* for additional clarification of responsibility)

Additionally, correspondence dated 07/08/11 between the Research Coordinator at Dr. Zhang's site and (b) (4) clarifies to Dr. Zhang's Research Coordinators that they are responsible for monitoring as seen in Exhibit 17 pg. 41.

Discussion with Management:
Dr. Zhang intends on sending a written response within 15 business days.

OBSERVATION 2
Failure to submit to FDA an annual report of the investigation.

Specifically, you did not submit to FDA an annual report for IND (b) (4) associated with Protocol # (b) (4) within 60 days of the anniversary date 02/05/11 that the IND went in effect. FDA received Protocol # (b) (4) under IND (b) (4) on 04/25/11. You did not submit an annual report in 2012, 2014, 2015, and 2016. The IND is still active and has not been closed.

Reference: 21 CFR 312.56(c)

Supporting Evidence and Relevance:
I asked Dr. Zhang if he has turned in annual report to FDA since 2013. He said no.

Dr. Zhang told me that an FDA Overdue Annual Report letters were being sent to his old location in Salt Lake City, Utah before he received the Overdue Annual Report letter at the correct address on 08/19/13. An annual report dated 12/17/13 was the only one submitted. At the time of this inspection, the IND was still active. Dr. Zhang stated that he plans on closing the IND. I informed him that since the IND is still active, he was required to send in annual report in 2014, 2015, and 2016. I continued to inform him that subjects were still enrolled in the clinical trial after the 2013 Annual Report that he submitted; therefore, it does not contain all study information after the trial was closed. I informed him that FDA sent another Overdue Annual Report letter dated 03/24/16. Dr. Zhang and Ms. Wen told me that they did not receive it and always reply immediately to any FDA correspondence they receive. I supplied Ms. Wen with a copy of the March 2016 Overdue Annual Report letter on 07/28/16.

Discussion with Management:

Dr. Zhang intends on sending a written response within 15 business days.

CLINICAL INVESTIGATOR

OBSERVATION 3
Failure to assure that an IRB was responsible for the initial and continuing review and approval of a clinical study.

Specifically, on December 7, 2012, the Investigational Review Board (IRB) for Protocol # (b) (4) notified the Principal Investigator "Effective immediately, suspension of new enrollment for ALL of the PI's active research trials at UCSD". On 08/26/13, the IRB lifted the enrollment suspension on the Principal Investigator. During the enrollment suspension period, the following subjects were enrolled in Protocol # (b) (4):

1) Subject (b) (6) was enrolled and received the study drug on 06/17/13. The subject conducted their Month 1 visit on 07/22/13 and Month 2 visit on 08/19/13. The study drug was not administered during the Month 1 and Month 2 visits.
2) Subject (b) (6) was enrolled and received the study drug on 08/12/13.
3) Subject (b) (6) was enrolled and received the study drug on 08/13/13.

Reference: 21 CFR 312.66

Supporting Evidence and Relevance:
The IRB letter regarding a report of serious and/or continuing noncompliance involving Dr. Kang Zhang to the FDA can be seen in Exhibit 37. The IRB letter states a report was created regarding an anonymous complaint that was filed under the university's Whistleblower hotline. The letter states, "A report provided to the HRPP [Human Research Protection Program] on November 27, 2012 for project (b) (4) titled (b) (4) " sponsored by (b) (4) . (IND (b) (4) , was discussed by a convened IRB at their December 6, 2012 meeting". Based on this letter, it appears that the complaint described in the letter was regarding treatment during the (b) (4) trial. The letter also incorrectly names (b) (4) as the sponsor. The letter continues to state that on December 7, 2012 the PI was informed of the complaint and the IRB actions of "Effective immediately, suspension of new enrollment for ALL of the PI's active research trials at UCSD". The letter states that the suspension of new enrollment is in effect until UCSD Audit and Management Advisory Services (AMAS) can conduct a thorough investigation. The allegations in the complaint are listed in the letter. All allegations involve genetic and tissue collection. IRB correspondence with Dr. Zhang, dated 08/26/13, stating the AMAS audit is completed and the enrollment suspension has been lifted can be seen in Exhibit 39. Based on the IRB correspondence records, the enrollment suspension period was December 7, 2012 to August 26, 2013.

On 07/15/16, I asked the Research Coordinator Cindy Wen if an IRB study suspension letter was sent to Dr. Zhang. Documentation that an IRB suspension letter dated 12/10/12 was not filed in the Regulatory Binder was listed in the UCSD Research Compliance Program audit results, dated 11/13/14. I also asked her if there was any documentation regarding the AMAS audit and the results. She told me the complaint resulting in the enrollment suspension and associated AMAS audit was regarding a different study that did not deal with a study drug. She told me the hold was for all studies so that is why the letter to the FDA regarding the enrollment suspension is in the regulatory binder. I asked her what the name of the study associated with the complaint. She told me it was called Genetic and Molecular Study for Eye Diseases. I told her that I do not see that study in Dr. Zhang's Curriculum Vitae. She said it was a research study which is why it is not required to be listed in Dr. Zhang's CV. Ms. Wen did not supply with any other records associated with the study suspension based on the rationale she told me on 07/15/16.

On 07/19/16, I informed Dr. Zhang that it appears that he violated the IRB enrollment suspension by enrolling Subjects (b) (6) between the observed suspension period of 12/07/12 – 08/26/12. He told me that he saw them and treated them per standard practice of care which was allowed by the IRB in the enrollment suspension letter. I told him that he was still seeing these subjects and treating them under the protocol. For the 3 subjects, an informed consent form was signed and visit procedures/monitoring was conducted per the protocol. During my record review of IRB correspondence, I observed Dr. Zhang's Cover Letter for Continuing Review for the (b) (4) study, dated 03/01/13, to state, "Enrollment in this study has been suspended per IRB Committee decision pending formal AMAS audit, as such, enrollment will remain suspended until further notice." (Exhibit 37 pg. 2). Based on the IRB correspondence, it appears that at the time Dr. Zhang understood and acknowledged that enrollment of new subjects were suspended for the (b) (4) study. Additionally, the IRB voted the continued approval of the study on 03/21/13 as documented in Exhibit 38 pg. 5. The continued approval letter states, "Please note that consent forms will not be released due to the enrollment hold on the study" (Exhibit 38 pg. 5). Since the enrollment hold was not lifted until 08/26/13, the

During the enrollment suspension period, the following subjects were enrolled in the (b) (4) study:

1) Subject (b) (6)
    - Subject (b) (6) signed the Informed Consent Form Version 4 on 06/17/13 as seen in Exhibit 62. Informed Consent Form Version 4 was not released by the IRB at the time it was signed (Exhibit 38 pg. 5).
    - On 06/17/13, Day 0 procedures were conduct documenting enrollment. The subject received the study drug during the Day 0 visit. Also, the blood sample collected for Genetic testing was conducted. Day 0 procedures can be seen in Exhibit 63.
    - During the enrollment suspension period, the subject conducted their Month 1 visit on 07/22/13 and Month 2 visit on 08/19/13 as seen in Exhibit 64. The study drug was not administered during the Month 1 and Month 2 visits.

2) Subject (b) (6)
   - Subject (b) (6) signed the Informed Consent Form Version 4 on 08/12/13 as seen in Exhibit 65. Informed Consent Form Version 4 was not released by the IRB at the time it was signed (Exhibit 38 pg. 5).
   - On 08/12/13, Day 0 procedures were conduct documenting enrollment. The subject received the study drug during the Day 0 visit. Also, the blood sample collected for Genetic testing was conducted. Day 0 procedures can be seen in Exhibit 66. Subject (b) (6) withdrew from the study on 08/13/13.

3) Subject (b) (6)
   - A Note to File stated Subject (b) (6) signed the Informed Consent Form Version 3 on 08/13/13 as seen in Exhibit 67. During the record review of the subject's binder, the signed ICF was missing. Ms. Wen was unable to locate the signed ICF (Refer to **Observation 6** for failure to maintain records during required retention period).
   - On 08/13/13, Day 0 procedures were conduct documenting enrollment. The subject received the study drug during the Day 0 visit. Also, the blood sample collected for Genetic testing was conducted. Day 0 procedures can be seen in Exhibit 68. The Month 1 visit was conducted after the enrollment suspension was lifted on 09/10/13

Discussion with Management:
Dr. Zhang intends on sending a written response within 15 business days.

OBSERVATION 4
An investigation was not conducted in accordance with the investigational plan.

Specifically, the following observations were deviations from the protocol:

A. All versions of the protocol had Section 4.1.2 Inclusion Criteria, Item 3, which required "(b) (4) " and, Item 4, which required "(b) (4) " to be included.
   a) The following subjects lost (b) (4) letters or less from baseline best vision:
      1) Subject (b) (6)
      2) Subject
      3) Subject
      4) Subject
      5) Subject

6) Subject (b) (6)
7) Subject

b) The following subjects had records with the following readings:
1) Subject (b) (6) was a non-(b) (4) patient whose Baseline visit, dated 08/12/11, documented visual acuity through pinhole of 20/60 in the right eye. The Day 0 visit, dated 11/28/11, documented visual acuity through pinhole of 20/50 in the right eye (study eye). The subject did not meet Inclusion Criteria Item 3 & 4.
2) Subject (b) (6) was a (b) (4) patient whose Baseline visit, dated 09/20/11, documented visual acuity 20/25 -2 in the right eye. The Day 0 visit, dated 02/13/12, documented visual acuity 20/32 -2. The subject did not meet Inclusion Criteria Item 3 & 4.
3) Subject (b) (6) was a (b) (4) patient whose Baseline visit is documented to occur on 03/25/13. The Day 0 visit occurred on 08/12/13. The subject did not meet Inclusion Criteria Item 3.

B. Amendment 2 and 3 of the protocol had section 4.1.2 Inclusion Criteria, Item 5, which required "Subjects who have not had an ETDRS to measure their baseline normal (pre-disease onset) may be included if they had a baseline Snellen VA of 20/20 or better, and it was done within 3 months of disease onset. Subject (b) (6) had a baseline Snellen VA of 20/25 for the study eye OD on 05/30/13; therefore, the subject did not meet inclusion criteria Item 5.

C. All versions of the protocol had section 4.1.1 Subject Selection referencing Appendix A documenting the study flow chart which required EDTRS BCVA, SD-OCT, and FA to be obtained at the Baseline period and Day 0/Screening visit. All (b) (4) subject records were reviewed. The following subjects were missing protocol required examinations needed to determine inclusion/exclusion criteria for the study:
1) Subject (b) (6) did not have EDTRS BCVA, SD-OCT, and FA conducted on the study eye for the Day 0/Screening visit.
2) Subject (b) (6) did not have SD-OCT and FA for the Baseline visit.
3) Subject did not have SD-OCT and FA for the Baseline visit.
4) Subject did not have EDTRS BCVA, SD-OCT, and FA for the Baseline visit.
5) Subject did not have SD-OCT and FA for the Baseline visit.
6) Subject did not have SD-OCT and FA for the Baseline visit.

D. All versions of the protocol section 4.5.2 Early Termination Assessments require (b) (4) ." An early termination visit was not conducted for Subjects (b) (6) .

Reference: 21 CFR 312.60

Supporting Evidence and Relevance:
During the review of the source documents, the following protocol deviations were observed:

A. All versions of the protocol had Section 4.1.2 Inclusion Criteria, Item 3, which required "(b) (4) " and, Item 4, which required "(b) (4) " to be included. The protocols can be seen in Exhibit 43-45. Additionally, when the drug supplier (b) (4) approved the protocol, minor suggestions were given for the inclusion criteria of the protocol, (b) (4) ." (Exhibit 17 pg. 75). Inclusion criteria Item 3 and 4 is necessary to be met in order to determine that the Primary Endpoint "To determine if patients treated early after diagnosis can return/maintain to their baseline pre-disease" is validated.

Many of the subject's files contained a Note to File for not meeting inclusion criteria. The rationale given was, "It was determined that [Subject initials] met all other inclusion and exclusion criteria and should still be enrolled in the study. The Inclusion and Exclusion Criteria are in the process of being modified for better evaluation of qualification for the study". I told Dr. Zhang that the rationale supplied does not address whether not meeting the inclusion criteria will affect the data integrity for meeting the protocol primary and secondary endpoints or the Subject's safety. Additionally, it states that the inclusion criteria will be modified for better evaluation of the study. Three (3) different versions of the Protocol were created and Inclusion Criteria Item 3 and Item 4 were never modified.

Dr. Zhang treated subject's despite not meeting the inclusion criteria because the drug is an approved drug for (b) (4) and he was treating them per Standard Practice of Care. I informed Dr. Zhang that the subject does not have to be included in the study in order to treat them under Standard Practice of Care with the drug; however, since he enrolled them in the study, he is required to meet protocol requirements.

a) The following subjects did not meet inclusion criteria Item 4; therefore, they did not lose (b) (4) letters or less from their baseline best vision:
   1) Subject (b) (6)
      - The Baseline best vision exam, dated 04/25/11, for the study eye OS was 20/40 as seen in Exhibit 69 & 70.
      - The Day 0 BCVA, dated 08/15/11, for the study eye OS was 20/50 as seen in Exhibit 71.
      - The Note to File for not meeting the inclusion criterion can be seen in

Exhibit 72. The Note to File states Subject (b) (6) had a loss of 4 letters of vision.

2) Subject (b) (6)

- The Baseline best vision exam, dated 09/28/11, for the study eye OS was 20/20 -1 as seen in Exhibit 73.
- The Day 0 BCVA, dated 10/06/11, for the study eye OS was documented as 20/25 on the Subject Info sheet as seen in Exhibit 74 pg. 1. Based on the source record documentation on the Subject Info sheet, the subject did not meet the inclusion criteria Item 4.
- When I reviewed the subject's record, their BCVA exam for the study eye OS on Day 0 was missing. The BCVA exam for the non-study eye OD and refraction eye exams were noted not done. It appears that the BCVA exam for the study eye OS was not done on the Day 0 visit dated 10/06/11. The BCVA exam is necessary to be administered in order to determine inclusion criteria are met. It appears that the study drug was administered without verifying if the subject met the inclusion criteria. The entire Day 0 visit record can be seen in Exhibit 74. Refer to **Observation 4 part C** below for issue regarding their missing records. Additionally, the subject suffered from a Serious Adverse Event associated with the injection of the study drug in the study eye on the Day 0 visit dated 10/06/11 due to the visit being rushed. Refer to **Safety and Adverse Event Reporting** section and Exhibit 22.

3) Subject (b) (6)

- The Baseline best vision exam, dated 04/23/12, for the study eye OD was 20/40 as seen in Exhibit 75 pg.1-2.
- The Day 0 BCVA, dated 08/13/12, for the study eye OD was 20/40 as seen in Exhibit 75 pg. 1. The BCVA results are documented on the Subject Info sheet.
- The Note to File for not meeting the inclusion criterion can be seen in Exhibit 75 pg. 3-4. The Note to File states Subject (b) (6) did not meet inclusion criterion of a loss of more than (b) (4) letters of vision from the baseline BCVA.

4) Subject (b) (6).
- The Baseline best vision exam, dated 04/24/12, for the study eye OS was 20/32 as seen in Exhibit 76 pg.1-3.
- The Day 0 BCVA, dated 08/31/12, for the study eye OS was 20/32 as seen in Exhibit 76 pg. 3-4.
- The Note to File for not meeting the inclusion criterion can be seen in Exhibit 76 pg. 5-7. The Note to File states Subject (b) (6) did not meet inclusion criterion of a loss of more than (b) (4) letters of vision from the baseline BCVA.

5) Subject (b) (6).
- The Baseline best vision exam for the study eye OD was 20/50 per the Subject Info sheet as seen in Exhibit 77 pg. 1. A Baseline BCVA was not obtained as referenced in **Observation 4 Section C**. The Subject was not a (b) (4) (b) (4) patient; therefore, the prior BCVA was not collected from the study.
- The Day 0 BCVA, dated 09/18/12, for the study eye OD was 20/50 as seen in Exhibit 77 pg. 1&3.

- The source document recording inclusion criterion loss of (b) (4) letters from baseline was not met can be seen in Exhibit 77 pg. 2. The source document states, "Inclusion approved by Dr. (b) (4) per observable disease +OCT". I could not determine if all other inclusion criteria were met due to the lack of Baseline records documenting baseline conditions (Refer to **Observation 4 Section C**). I did not observe a separate Note to File in the subject record documenting the rationale for enrolling the subject in the study despite not meeting Inclusion Criterion Item 4

6) Subject (b) (6).
- The Baseline best vision exam, dated 07/03/12, for the study eye OS was 20/20 per the Subject Info sheet as seen in Exhibit 78 pg. 1. The study site did not have the Baseline BCVA for the study eye OS. The lack of record was not documented in the FDA 483.
- The Day 0 BCVA, dated 09/25/12, for the study eye OS was 20/25 as seen in Exhibit 78 pg. 1-2.
- The Note to File for not meeting the inclusion criterion can be seen in Exhibit 78 pg. 3-5. The Note to File states Subject (b) (6) did not meet inclusion criterion of a loss of more than (b) (4) letters of vision from the baseline BCVA.

7) Subject (b) (6)
   - The Baseline best vision exam, dated 07/16/13, for the study eye OS was 20/40 as seen in Exhibit 68 pg. 1, 19-20. The ETDRS Chart with Aquity Equivalents Adjusted for 2 Meters record documents for the study eye OS the visual acuity is 20/40-1 through pin hole Exhibit 68 pg. 19. Without pinhole, the whole row of 20/50 is circled.
   - The Day 0 BCVA, dated 08/13/13, for the study eye OS was documented as 20/63 on the Subject Info form and Retina ETDRS Progress Report as seen in Exhibit 68 pg. 1 & 21. The ETDRS Chart with Acuity Equivalents Adjusted for 2 Meters record documents each letter to be circled at 20/40 and 20/50 as seen in Exhibit 68 pg. 21. I asked Ms. Wen what that means and she said that when each letter is circled instead of the entire row being circled, it means that the subject could see those letters through pinhole. Without pinhole, the whole row of 20/63 is circled. Based on the ETDRS Chart with Acuity Equivalents Adjusted for 2 Meters record for the Baseline visit and Day 0 visit, the subject appears to not meet inclusion criterion Item 4.

b) The following subjects did not meet Inclusion Criteria Item 3 and 4 or Inclusion Criterion Item 3:
   1) Subject (b) (6)
      - Subject (b) (6) was a non-(b) (4) patient whose Baseline visit, dated 08/12/11, documented visual acuity through pinhole of 20/60 for the study eye OD as seen in Exhibit 79 pg. 1&3.
      - The Day 0 visit, dated 11/28/11, documented visual acuity through pinhole of 20/50 in study eye OD as seen in Exhibit 79 pg. 1 & 4-5.
      - The subject did not meet Inclusion Criteria Item 3 since the Baseline exam was 3 months and two weeks prior to the Day 0 exam. The subject did not meet Inclusion Criteria Item 4 because the subject did not lose more than (b) (4) letters of vision from the baseline. Lack of meeting Inclusion Criteria Item 3 and 4 is documented in the Note to File seen in Exhibit 79 pg. 6-8. Documentation that the subject was not a (b) (4) patient is seen in the Progress Notes dated 11/28/11 as seen in Exhibit 79 pg. 2. The Progress Notes state the subject visited Dr. Zhang for a standard of care visit.
   2) Subject (b) (6)
      - Subject (b) (6) was a (b) (4) patient whose Baseline visit, dated 09/20/11, documented visual acuity 20/25 -2 for the study eye OD as seen in Exhibit 80 pg. 3. The Snellen visual acuity (VA) was 20/32 as documented on the Subject Info sheet as seen in Exhibit 80 pg. 1.
      - The Day 0 visit, dated 02/13/12, documented visual acuity 20/32 -2 with a Snellen VA result of 20/40 as seen in Exhibit 80 pg. 4. The Snellen VA

was 20/40 as documented on the Subject Info sheet and Day 0 BCVA exam as seen in Exhibit 80 pg. 1.

- The subject did not meet Inclusion Criteria Item 3 since the Baseline exam was approximately 5 months prior to the Day 0 exam. The subject did not meet Inclusion Criteria Item 4 because the subject did not lose more than (b) (4) letters of vision from the baseline. Dr. Zhang documented that the subject met all inclusion criteria as seen in Exhibit 80 pg. 5.

3) Subject (b) (6)
   - Subject (b) (6) was a (b) (4) patient whose Baseline visit was conducted on 03/25/13 as seen in Exhibit 66 pg. 1 & Exhibit 81. The Day 0 visit occurred on 08/12/13 as seen in Exhibit 66 pg. 1 &19. The subject did not meet Inclusion Criteria Item 3 since the Baseline exam was approximately 5 months prior to the Day 0 visit.

B. The (b) (4) Protocol versions Amendment 2 and 3 section 4.1.2 Inclusion Criteria, Item 5, states, (b) (4) (Exhibit 44 and 45). Subject (b) (6) had a baseline Snellen VA of 20/25 for the study eye OD, dated 05/30/13, as seen in Exhibit 82. The eye exam medical record documents the Refraction OD exam to be 20/25 and the Visual Acuity OD exam to be 20/30. The Day 0 best visual acuity exam for the study eye OD was 20/32 -2, dated 06/17/13, as seen in Exhibit 63 pg. 15-16. The subject did not meet inclusion criteria Item 5 since the baseline Snellen VA exam was not 20/20 or better.

C. All versions of the protocol had section 4.1.1 Subject Selection referencing Appendix A documenting the study flow chart which required EDTRS BCVA, SD-OCT, and FA to be obtained at the Baseline period and Day 0/Screening visit as seen in Exhibit 43-45. All (b) (4) subject records were reviewed. The following subjects were missing protocol required examinations needed to determine inclusion/exclusion criteria for the study:

1) Subject (b) (6) did not have EDTRS BCVA, SD-OCT, and FA conducted on the study eye for the Day 0/Screening visit dated 10/06/11. I collected the entire Day 0 visit subject records dated 10/06/11 as seen in Exhibit 74. The Day 0 ETDRS BCVA exam sheet for the study eye OS was not included in the record. The Day 0 ETDRS BCVA exam sheet for the non-study eye and Refraction exam sheet for both eyes are crossed out with a note stating “not done” initialed by Cindy Wen on 07/30/15 as seen in Exhibit 74 pg. 19-21. Additionally, SD-OCT and FA were not taken as indicated in the source document seen in Exhibit 74 pg.8.

2) Subject (b) (6) did not have SD-OCT and FA for the Baseline visit. I asked Ms. Wen for the records multiple times throughout the inspection. She told me that the SD-

OCT and FA were not collected for every subject for the Baseline visit. She told me the doctor referred to the subject's medical history or records to determine whether the subject was diagnosed with (b) (4) in the study eye at the time of the Baseline visit. Subject (b) (6) was not part of the (b) (4) study (Exhibit 79 pg. 2-3); therefore, an SD-OCT and FA was not taken during the Baseline visit since it was a standard practice of care visit.

3) Subject (b) (6) did not have SD-OCT and FA for the Baseline visit. I asked Ms. Wen for the records multiple times throughout the inspection. She told me that the SD-OCT and FA were not collected for every subject for the Baseline visit. She told me the doctor referred to the subject's medical history or records to determine whether the subject was diagnosed with (b) (4) in the study eye at the time of the Baseline visit. Subject (b) (6) was enrolled in the (b) (4) study; however, Ms. Wen did not supply with SD-OCT and FA from the previous (b) (4) visit. It appears that SD-OCT and FA was not conducted during the Baseline visit. Baseline visit records can be seen in Exhibit 76.

4) Subject (b) (6) did not have EDTRS BCVA, SD-OCT, and FA for the Baseline visit. I asked Ms. Wen for the records multiple times throughout the inspection. She told me that the SD-OCT and FA were not collected for every subject for the Baseline visit. She told me the doctor referred to the subject's medical history or records to determine whether the subject was diagnosed with (b) (4) in the study eye at the time of the Baseline visit. She was unable to determine how the Baseline information was collected for Subject (b) (6) since the study site did not have any of the subject's baseline records on hand. According to the Subject Info sheet seen in Exhibit 77 pg. 1, the Baseline BCVA for the study eye OD was 20/50 on 06/18/12. On 07/28/16, Ms. Wen told me that she does not have any records to support the exam results recorded in the source document. Subject (b) (6) was not enrolled in the (b) (4) study.

5) Subject (b) (6) did not have EDTRS BCVA, SD-OCT, and FA for the Baseline visit. I asked Ms. Wen for the records multiple times throughout the inspection. She told me that the SD-OCT and FA were not collected for every subject for the Baseline visit. She told me the doctor referred to the subject's medical history or records to determine whether the subject was diagnosed with (b) (4) in the study eye at the time of the Baseline visit. She was unable to determine how the Baseline information was collected for Subject (b) (6) since the study site did not have any of the subject's baseline records on hand. According to the Subject Info sheet seen in Exhibit 78 pg. 1, the Baseline BCVA for the study eye OD was 20/20 on 07/03/12. On 07/28/16, Ms. Wen told me that she does not have any records to support the exam results recorded in the source document. Subject (b) (6) was not enrolled in the (b) (4) study.

6) Subject (b) (6) did not have SD-OCT and FA for the Baseline visit. I asked Ms. Wen

for the records multiple times throughout the inspection. She told me that the SD-OCT and FA were not collected for every subject for the Baseline visit. She told me the doctor referred to the subject's medical history or records to determine whether the subject was diagnosed with (b) (4) in the study eye at the time of the Baseline visit. Subject (b) (6) was not part of the (b) (4) study; therefore, an SD-OCT and FA was not taken during the Baseline visit since it was a standard practice of care visit. The Baseline visit, dated 05/30/13, was an eye exam conducted on the subject as seen in Exhibit 82.

D. All versions of the protocol section 4.5.2 Early Termination Assessments require (b) (4) ." as seen in Exhibits 43-45. During the record review, I did not observe an early termination visit to be conducted for the following subjects:

- Subject (b) (6) – Ms. Wen told me that an early termination visit was not conducted for Subject (b) (6) because the subject withdrew due to travel distance and inconvenience. I told her that I did not see any note to files documenting the protocol deviation. Subject (b) (6) 's Subject Info Sheet and Progress Notes showing that the Month 9 visit, dated 05/29/12, was the last visit conducted can be seen in Exhibit 69 and Exhibit 83 pg. 2. Subject (b) (6) 's call log documenting on 06/07/12 the subject stated they wished to withdraw from the trial can be seen in Exhibit 83 pg. 1.
- Subject (b) (6) – Ms. Wen told me that an early termination visit was not conducted for Subject (b) (6) because the subject suffered from a Serious Adverse Event (SAE) associated with the Day 0 study drug injection by Dr. Zhang and did not want to participate in the study any longer. Documentation of Subject (b) (6) 's complaint regarding the SAE and wish to withdraw from the study can be seen in Exhibit 22. I told her that I did not see any note to files documenting the protocol deviation.
- Subject (b) (6) – Ms. Wen told me that an early termination visit was not conducted for Subject (b) (6) because the subject entered hospice care for uncontrolled type 2 diabetes. I told her that I did not see any note to files documenting the protocol deviation. The MedWatch report documenting withdrawal from the study due to entering hospice care can be seen in Exhibit 24. Subject (b) (6) 's Subject Info sheet documenting the Month 1 visit was the last visit conducted can be seen in Exhibit 80 pg. 1.
- Subject (b) (6) – Ms. Wen told me that an early termination visit was not conducted for Subject (b) (6) because the subject withdrew the day after the Day 0 visit due to personal reasons. I told her that I did not see any note to files documenting the protocol deviation. Documentation of the withdrawal request for the study and that the Day 0 visit was the last visit conducted can be seen in Exhibit 66 pg. 1-2.

Discussion with Management:
Dr. Zhang intends on sending a written response within 15 business days.

OBSERVATION 5
The informed consent document does not include the required statement: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

Specifically, all versions of your informed consent form does not contain the required clinical trial statement.

Reference: 21 CFR 50.25(c)

Supporting Evidence and Relevance:

A review of all IRB approved versions of the Informed Consent Form used during the study was conducted. The required www.Clinical Trial.gov statement listed above was not documented in all versions of the Informed Consent as seen in the following Exhibits:

- Informed Consent Form Version 2 – Exhibit 51
- Informed Consent Form Version 3 – Exhibit 52
- Informed Consent Form Version 4 – Exhibit 53

I pointed out the observation to Ms. Wen on 07/28/16. She asked me if the statement was required since the study was using an approved study drug. I explained to her that an IND was submitted documenting this study as a Phase 1 Clinical Trial; therefore, they are required to follow the regulations. I showed her the regulations for Informed Consent Forms in my copy of 21 CFR 50 book. Then, I showed her 21 CFR 50.25(c) where the requirement is listed. She argued that the study should not have been under an IND because the investigational drug is an approved drug. I told her an approved drug can still be investigated under different indications which would require an IND submission. As discussed at the start of the inspection, I told her that it is not my responsibility to evaluate whether an IND submission should have been submitted. Since an IND was submitted, I am evaluating Dr. Zhang as a Sponsor-Investigator per the regulations.

Discussion with Management:

Dr. Zhang intends on sending a written response within 15 business days.

OBSERVATION 6
Investigational records were not retained for a period of two years following discontinuance of the investigation and notification of FDA.

Specifically, the following records were not retained:

E. Refrigerated study drug temperature log from 07/19/13 to the end of the study.
F. Informed Consent Form (ICF) signed by Subject (b) (6) on 07/16/13. The source document contains a Note to File stating the subject signed the incorrect version of the ICF; however, the ICF form cannot be located.
G. Subject (b) (6) 's source documents did not contain SD-OCT and FA records for the Month 12 visit, despite documentation of it being conducted.
H. Subject (b) (6) 's source documents did not contain SD-OCT and FA records for the Baseline visit, despite documentation of it being conducted during the previous (b) (4) study visit.

Reference: 21 CFR 312.62(c)

Supporting Evidence and Relevance:

E. The study drug was required to be stored from (b) (4) per all versions of the protocol; therefore, storage temperature was required to be documented. The study site did not have refrigerator temperature log records past 07/19/13 as seen in Exhibit 58. I asked Ms. Wen if there are records past 07/19/13. She told me that records were created but she is unable to find them.

F. Subject (b) (6) 's subject binder contained a Note to File stating the incorrect version of the ICF was administered and signed as seen in Exhibit 67. The Informed Consent Form signed by Subject (b) (6) was not in the subject binder. I asked Ms. Wen if she could locate the ICF signed by Subject (b) (6) . She was unable to find the record.

G. Subject (b) (6) 's Month 12 source document, dated 09/09/13, shows that SD-OCT and FA protocol procedures were conducted during the visit as seen in Exhibit 84 pg. 1-2. However, the SD-OCT and FA records were not in subject's study binder. I asked Ms. Wen for the records. She was unable to find the records for me.

H. Subject (b) (6) is documented to be recruited from the (b) (4) study as seen in Exhibit 66 pg. 2. During the (b) (4) study, SD-OCT and FA is conducted. The subject's last (b) (4) visit is used as the Baseline visit. I requested Subject (b) (6) (b) (4) source documents. Ms. Wen was unable to locate the file and supply it to me during the inspection. The Baseline SD-OCT and FA records are necessary to determine if the subject met inclusion criteria.

Discussion with Management:
Dr. Zhang intends on sending a written response within 15 business days.

OBSERVATION 7
Investigational drug disposition records are not adequate with respect to quantity.

Specifically, the disposition of the expired study drug is not adequately documented for the following:

I. A destruction record, dated 05/09/12, documenting destruction via chemical waste of (b) (4) of the expired study drug does not document the lots of the expired investigational drugs destroyed. Additionally, the study drug accountability log documents (b) (4) units of Lot # (b) (4) expiring on (b) (4), (b) (4) units of Lot # (b) (4) expiring on (b) (4), and (b) (4) units of Lot # (b) (4) expired on (b) (4), totaling (b) (4) units of the investigational drug with an expiration date prior to 05/09/12. (b) (4) units are unaccounted for.

J. You do not have documentation of the accountability of the received (b) (4) unit of unused, expired investigational drugs, Lot (b) (4), expiration date (b) (4).

Reference: 21 CFR 312.62(a)

Supporting Evidence and Relevance:
The study drug accountability log can be seen in Exhibit 60. Investigational Drug Request and Receiving records can be seen in Exhibit 59. The date received, amount of the study drug, and lot # of the study drug received is accurately documented in the log.

I. The study drug accountability log shows the following unused study drugs: (b) (4) units of Lot # (b) (4) expiring on (b) (4), 4 units of Lot # (b) (4) expiring on (b) (4), and (b) (4) units of Lot # (b) (4) expired on (b) (4) (Exhibit 60). The study site had documentation that (b) (4) vials of expired (b) (4) were destroyed on 05/09/12 as seen in Exhibit 61. The study drug accountability log documents (b) (4) units of expired study that would have been on hand on 05/09/12. Additionally, the destruction record does not document the lot number and amount per lot that was destroyed. There is no assurance that destruction record supplied to me is associated with the expired study drug supplied for use on the (b) (4) study. Additionally, there are (b) (4) units that are unaccounted for if the destruction record is associated with expired study drugs on hand that was supplied for the (b) (4) study.

J. The study drug accountability log documents (b) (4) unit of unused, expired investigational drugs, Lot (b) (4), expiration date (b) (4) (Exhibit 60). I asked Ms. Wen about the unaccounted for units. She stated that the expired unused study medication is stored at ambient temperature in storage somewhere. I asked her if I could see the expired, unused study medication before the inspection close out. She found the (b) (4) units of unused, expired study drug Lot (b) (4), but did

not find the (b) (4) units of Lot (b) (4) .

Discussion with Management:
Dr. Zhang intends on sending a written response within 15 business days.

REFUSALS
No refusals were encountered.

GENERAL DISCUSSION WITH MANAGEMENT
During the inspection and close-out meeting, the following issues were discussed with Dr. Zhang and Ms. Wen:

1) Lack of Financial Disclosures from Sub-Site Principal Investigators
On 07/19/16, I asked Dr. Zhang if he obtained financial disclosures from the sub-site Principal Investigators prior to starting the study. I informed him that I did not see any documentation in the Sponsor binder supplied to me. He told me that he will have Ms. Wen look for the records. On 07/28/16, Ms. Wen supplied me with an e-mail correspondence dated 07/19/16 with an employee from the (b) (4) site. It stated, "financial disclosures, as the investigators had nothing to disclose, the IRB did not require any disclosure form" (Exhibit 14). Ms. Wen was unable to locate any financial disclosure records for Dr. (b) (4) . I informed Dr. Zhang that Sponsor responsibilities include obtain financial disclosures from all Clinical Investigators (CI) on the study. I told him that the regulations require a financial disclosure form to be filled out, even if the CI has nothing to report. He told me that he understands.

2) Lack of Adverse Event reporting in Subject's Adverse Event Log
I informed Dr. Zhang that during the record review, I observed adverse events to be reported during the post-injection phone call and documented on the source document record. I informed him that the adverse event was not always documented in the subject's adverse event log. I continued to tell him that it is important to document all adverse events that have occurred in the adverse event log in order to document that the adverse event was monitored and addressed by the clinical investigator. For example, during the Month 9 visit dated 06/03/13, Subject (b) (6) reported they saw black dots in the study eye for 3-4 hours after the injection (Exhibit 85 pg. 1). This was not documented in the Adverse Event Log or reviewed during the next visit dated 07/08/13 as seen in Exhibit 85 pg. 2-4. Dr. Zhang replied that he understood the discussion item.

3) Multiple Note to File Protocol Deviations for Missed Study Drug Administration and IOP Exams
I informed Dr. Zhang that during the record review, I observed multiple Note to Files for multiple different subjects regarding missed study drug administration and post dose Intraocular Pressure (IOP) Exams. I informed Dr. Zhang that treated the subject with the study drug per the protocol requirements is necessary to obtain accurate information regarding meeting the Primary and

Secondary Endpoint. Additionally, post IOP exams are necessary for the subject's safety and are required per the protocol and Investigator Brochures.

Section 3.1 Description of the Study in all versions of the protocol state, (b) (4) (Exhibits 43-45). The study drug was observed to be withheld for the following 4 subjects because there was no evidence of fluid on the SD-OCT during the study visit; however, the BCVA for the study eye did not return to baseline visual acuity (b) (4).

- **Subject** (b) (6) Baseline BCVA for the study eye OD is 20/40 (Exhibit 75). The study eye was not administered with the study drug during the following visits despite the study eye not returning to baseline visual acuity:
    - Month 1, dated 09/10/12, had a BCVA in OS of 20/50 – Exhibit 86 pg.1-3
    - Month 6, dated 02/11/13, had a BCVA in OS of 20/50 – Exhibit 86 pg.4-6
    - Month 7, dated 03/25/13, had a BCVA in OS of 20/50 – Exhibit 86 pg. 7-9

- **Subject** (b) (6) Baseline BCVA for the study eye OS is 20/32 (Exhibit 76). The study eye was not administered with the study drug during the following visits despite the study eye not returning to baseline visual acuity:
    - Month 3, dated 12/04/12, had a BCVA in OS of 20/40 – Exhibit 87 pg.1-5
    - Month 6, dated 03/05/13, had a BCVA in OS of 20/40 – Exhibit 87 pg. 6-8
    - Month 9, dated 05/28/13, had a BCVA in OS of 20/32 – Exhibit 87 pg. 9-11

- **Subject** (b) (6) Baseline BCVA for the study eye OD is 20/50 (Exhibit 77). The study eye was not administered with the study drug during the following visits despite the study eye not returning to baseline visual acuity:
    - Month 3, dated 12/18/12, had a BCVA in OD of 20/40-2 – Exhibit 88

- **Subject** (b) (6) Baseline BCVA for the study eye OS is 20/20 (Exhibit 78). The study eye was not administered with the study drug during the following visits despite the study eye not returning to baseline visual acuity:
    - Month 3, dated 01/08/13, had a BCVA in OS of 20/40 – Exhibit 89 pg.1-3
    - Month 4, dated 02/05/13, had a BCVA in OS of 20/32 – Exhibit 89 pg. 4. Documentation that the study drug was not administered in the study eye during the visit can be seen in Exhibit 78 pg. 1.
    - Month 5, dated 03/05/13, had a BCVA in OS of 20/32 – Exhibit 89 pg. 5-8

Section 1.5 Clinical Experience with (b) (4) in all versions of the protocol states, (b) (4) (Exhibits

43-45). A post-injection intraocular pressure exam was not conducted with no explanation for the following two subjects:

- **Subject** (b) (6) : Post-Injection IOP was not conducted during study visit Month 10, dated 07/30/13, and Month 11, dated 09/03/13 as seen in Exhibit 90. A Note to File stating there was no explanation of the deviation was included in the subject records.
- **Subject** (b) (6) : Post-Injection IOP was not conducted during study visit Day 0, dated 06/17/13 as seen in Exhibit 63 pg. 13. The record documents that post injection IOP was not recorded in error.

4) Failure to forward Investigator Brochures to Sub-sites

During the inspection, I asked Dr. Zhang if the Investigator Brochures he received were forwarded to the study sites and documentation of it. Dr. Zhang stated that (b) (4) supplied him with the Investigator Brochures and he was responsible for supplying it to the sub-sites. He told me he thinks he supplied the Investigator Brochures (IB) to the sub-sites. Documentation that Dr. Zhang received Investigator Brochure Version 9-12 can be seen in Exhibit 18. Dr. Zhang's site was unable to supply me with any documentation that the IB was supplied to the sub-sites. Ms. Wen stated the correspondence supplied to me seen in Exhibits 11, 16, and 17 are everything the site has. Documentation that the IB was forwarded to the sub-sites was not found in the correspondence records. I informed Dr. Zhang that Sponsor responsibilities include supplying all Principal Investigators with information regarding the study which includes the Investigator Brochure. He responded that he understands.

EXHIBITS COLLECTED

1 Research Agreement with (b) (4) , 16 pages
2 IND from Dr. Kang Zhang, 2 pages
3 Letter to FDA regarding (b) (4) IND submission, 1 page
4 Letter to FDA regaring (b) (4) IND submission, 1 page
5 FDA response to the IND submission, 3 pages
6 Overdue Annual Report Notice , 3 pages
7 2013 Annual Report, 17 pages
8 FDA 1572 Kang Zhang, 2 pages
9 FDA 1572 (b) (4) , 2 pages
10 FDA 1572 (b) (4) , 2 pages
11 Correspondence with Dr. (b) (4) site & IRB records, 28 pages
12 UCSD agreement with Dr. (b) (4) , 5 pages
13 www.ClinicalTrials.gov submission, 7 pages
14 Lack of Financial Disclosure for CRC site e-mail, 2 pages
15 FDA 1571 Dr. (b) (4) , 2 pages
16 Correspondence with Dr. (b) (4) site & IRB records, 75 pages

17 Sponsor correspondence with (b) (4) and sub-sites, 57 pages
18 Investigator Brochure receiving records, 13 pages
19 Investigator Brochure Version 9, 278 pages
20 Investigator Brochure Version 10, 382 pages
21 Investigator Brochure Version 11, 347 pages
22 Subject (b) (6) SAE Reporting, 22 pages
23 Subject SAE Report, 10 pages
24 Subject Medwatch Report, 5 pages
25 Study Closure E-mail, 2 pages
26 Kang Zhang's Curriculum Vitae, 30 pages
27 Delegation Log, 5 pages
28 Enrollment Log, 2 pages
29 IRB initial approval , 29 pages
30 IRB approval pending list , 2 pages
31 IRB project approval notice, 14 pages
32 IRB Conflict of Interest acknowledgement, 4 pages
33 IRB complaint receipt for (b) (6) SAE, 23 pages
34 IRB Protocol Deviation Acknowledgment, 2 pages
35 IRB Continued Review approval , 5 pages
36 IRB Protocol Amendment approval, 5 pages
37 IRB Enrollment Suspension for PI Zhang, 3 pages
38 IRB protocol amendment approval , 15 pages
39 IRB enrollment suspension lift, 2 pages
40 IRB continued review approval , 7 pages
41 IRB lack of renewal notice, 2 pages
42 IRB study withdrawn notice, 1 page
43 Protocol Version 1, 36 pages
44 Protocol Version 2, 18 pages
45 Protocol Version 3.5, 20 pages
46 IRB Letter of Assurance, 1 page
47 IRB Personnel Amendment approvals, 22 pages
48 IRB correspondence List, 6 pages
49 UCSD Research Compliance Program audits, 9 pages
50 Late response to IRB letter, 16 pages
51 ICF Version 2, 7 pages
52 ICF Version 3, 8 pages
53 ICF version 4, 8 pages
54 Dr. Zhang's Financial Disclosure Form, 5 pages
55 (b) (4) temperature deviation notification, 4 pages
56 November study drug temperature excursion, 1 page
57 September study drug temperature excursion, 1 page
58 Last page of the refrigerator temperature log, 1 page
59 Study drug receipt records, 18 pages
60 Study Drug Accountability Log, 9 pages

61 Study drug destruction record, 1 page
62 ICF for Subject (b) (6) , 17 pages
63 Subject (b) (6) Day 0, 16 pages
64 Subject Month 1 and Month 2 visit, 30 pages
65 Subject ICF, 13 pages
66 Subject Day 0, 23 pages
67 Subject Note to File for ICF, 3 pages
68 Subject Day 0, 21 pages
69 Subject Subject Info Sheet, 1 page
70 Subject Baseline BCVA OS study eye, 1 page
71 Subject Day BCVA OS study eye, 1 page
72 Subject Note to File for Inclusion Critieria, 2 pages
73 Subject Baseline visit records, 2 pages
74 Subject Day 0 records, 21 pages
75 Subject Inclusion Criterion records, 4 pages
76 Subject Inclusion Criteria, 7 pages
77 Subject Inclusion Criteria, 3 pages
78 Subject Inclusion Criteria, 5 pages
79 Subject Inclusion Criteria, 8 pages
80 Subject Inclusion Criteria, 5 pages
81 Subject Baseline visit, 2 pages
82 Subject Baseline visit, 1 page
83 Subject call log and progress notes, 2 pages
84 Subject Month 12 visit, 8 pages
85 Subject Adverse Event Reporting , 4 pages
86 Subject Missed Study Drug Administration, 9 pages
87 Subject Missed Study Drug Administration, 11 pages
88 Subject Missed Study Drug Administration, 3 pages
89 Subject Missed Study Drug Administration, 8 pages
90 Subject Missed Post Injection IOP exam, 4 pages

ATTACHMENTS

1 FDA 463a, Affidavit, not signed by Kang Zhang, M.D., Ph.D., 2 pages
2 FDA 482 issued to Cindy H. Wen Clinical Research Coordinator, on 07/14/16, 3 pages
3 Issued 483
4 Assignment Memo, 7 pages

X Natalie J. Ayoub -S Digitally signed by Natalie J. Ayoub -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000404802, cn=Natalie J. Ayoub -S Date: 2016.08.25 11:55:12 -07'00'

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